Docket No.: 223002107200
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Nichòlas M. VALIANTE, Jr.

Application No.: 10/814,480 Confirmation No.: 9427

Filed: March 29, 2004 Art Unit: 1617

For: USE OF SMALL MOLECULE COMPOUNDS FOR IMMUNOPOTENTIATION Examiner: Y. S. Chong

DECLARATION OF NICHOLAS M. VALIANTE PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Nicholas M. Valiante, declare as follows:

1. I am the inventor of the above-referenced patent application, and am familiar with the contents thereof.

2. I hold a Ph.D. in Immunology and I am currently Head of Immunology for Novartis Vaccines & Diagnostics in the United States. I am experienced in and remain actively engaged in the field of pharmaceutical research and development. I have been working in the field of vaccine discovery for over 11 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

3. The present invention is directed in part towards pharmaceutical vaccine compositions comprising a small molecule immune potentiator (SMIP) compound of formula XXI and an antigen, where the compound of formula XXI functions as a vaccine adjuvant and is present in an amount effective to enhance the immune response to the antigen.

4. I understand that the Office has rejected the pending claims because they are alleged to be obvious over Chamberlain et al. (US 2005/023083 A1) in view of Klaviniskis et al. (US 2003/0147923).

5. Chamberlain et al. (US 2005/023083 A1) describe the use of benzimidazole-substituted diaminopyrimidine compounds for treating disorders mediated by VEGFR-2 and TIE-2 kinases and those relating to angiogenesis, such as cancer. Chamberlain et al. describe oil-in-water emulsions as carriers for the oral administration of the disclosed compounds. However, oil-in-water formulations of small molecule drugs are not necessarily suitable for vaccine formulations. Chamberlain et al. mention use of their compounds in combination with other cancer therapeutics, such as chemotherapeutic, hormonal or antibody agents. None of these 'therapeutic agents' would be expected to work by eliciting an immune response, so one of skill in the art would have no reason to combine Chamberlain's compounds with an antigen or immunogenic composition.

6. Klaviniskis et al. (US 2003/0147923) disclose vaccine compositions containing a bacterium spore (*B. subtilis*) that acts as an adjuvant to enhance an immune response, when combined with an antigen. Various antigens are described, and at least some such compositions are said to be useful to treat certain cancers.

7. Because the compounds of Chamberlain et al. and the vaccine compositions of Klaviniskis et al. were generally referred to as useful for treating cancer, the Office has alleged that it would have been obvious to combine a compound of Formula XXI with a vaccine composition of Klaviniskis et al. to arrive at a composition within the scope of the claims.

8. From my personal knowledge of the field of vaccine formulations, I state that it is well known in the art that vaccine compositions require specialized formulations and are not ordinarily combined with small molecule therapeutic agents. I further state that practitioners of this art would recognize that mixing a vaccine and a therapeutic agent into a single composition would generally be inappropriate and undesirable, because it would limit the ability to optimize the frequency and route of administration for each agent.

9. In addition, I state that skilled practitioners would recognize the likelihood that combining a vaccine composition and a therapeutic agent could lead to adverse drug interactions. For example, an adjuvant in a vaccine composition could cause an immune reaction to a drug physically admixed with the vaccine composition. For at least these reasons, a skilled practitioner in this art would not combine a vaccine and a small molecule drug like the compounds disclosed by Chamberlain et al. into a single composition just so they can be administered as a single composition.

10. Moreover, I state that those of skill in the art would recognize that concurrent treatment with a vaccine and another therapeutic agent does not require mixing these materials together, and in view of the expected differences in administration and the potential for adverse interactions, they ordinarily would *not* be mixed by a person of ordinary skill. Where concurrent treatment is desired, a skilled practitioner would preferably administer each agent to a single patient *separately*, allowing each agent to be delivered under optimal conditions.

11. The present claims require an amount of a compound of formula XXI that is effective to enhance an immune response. One of ordinary skill in the art can readily determine this amount. However, it is not possible to know whether the amount of Chamberlain's drug required to produce a therapeutic effect (such as the treatment of cancer) would be sufficient to provide an enhanced immune response to an antigen.

12. The specification demonstrates that compounds of formula XXI produce an unexpected immune-stimulating response or agonistic to an antigen in the claimed compositions. These effects could not have been expected from the cited documents, which disclose only antiangiogenic or antagonistic activity for the compounds of Chamberlain et al.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that

such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Cambridge, Massachusetts on 4/30/2009

Nicholas M. Valiante, Ph.D.

Nicholas M. Valiante, Ph.D.

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Born: June 23, 1965; Citizenship: U.S.

Education:

1983-1987	**Boston University, Boston, MA** B.A. Evolutionary Biology
1989-1994	**University of Pennsylvania, Philadelphia, PA** Ph.D. Immunology

Awards:

1983-1987	Boston University Board of Trustees Scholarship
1989-1991	University of Pennsylvania Immunology Fellowship
1991-1994	The Wistar Institute Fellowship
1994	Stanford University Medical School Fellowship
1994-1997	Cancer Research Institute of New York Fellowship
1995-1997	Leukemia Society of America Translational Research Award

Positions Held:

1987-1988	**E.I. du Pont de Nemours & Co., Billerica, MA** Research Assistant: Immunology
1988-1989	**Harvard Medical School, Boston, MA** Research Assistant: Immunology and Rheumatology
1989-1994	**University of Pennsylvania, Philadelphia, PA** Graduate Student: Immunology
1994-1997	**Stanford University Medical School, Stanford, CA** Post-Doctoral Researcher: Structural Biology and Immunology
1998-2001	**Chiron, S.p.A. (IRIS Research Institute), Siena, Italy** Senior Scientist: Immunology/Virology Department
2001-2002	**Chiron, S.p.A. (IRIS Research Institute), Siena, Italy** Associate Director: Immunology/Virology Department
2003-2006	**Chiron Corporation Vaccines Research, Emeryville, CA** Associate Director/Project Leader: Vaccine Adjuvants
2006-2007	**Novartis Vaccines Research, Emeryville, CA** Associate Director/Global Project Leader: SMIP/TLR Platform
2007-2008	**Novartis Vaccines Research, Emeryville, CA** Director/Global Project Leader: SMIP/TLR Platform
2008-Present	**Novartis Vaccines Research, Cambridge, MA** Director/Head of Immunology (U.S.)